WHAT IS CLAIMED IS:

1. A method for enhancing the immunostimulatory effect of an antigen encoded by nucleic acid contained in a nucleic acid construct comprising:

   determining the CpG-N and CpG-S motifs present in the construct; and

   removing neutralizing CpG (CpG-N) motifs and optionally inserting stimulatory CpG (CpG-S) motifs in the construct,

   thereby producing a nucleic acid construct having enhanced immunostimulatory efficacy.

2. The method of claim 1, wherein the CpG-N motifs are removed by site-specific mutagenesis.

3. The method of claim 1, wherein the CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

4. The method of claim 1, wherein the nucleic acid construct is an expression vector.

5. The method of claim 4, wherein the vector is a plasmid.

6. The method of claim 4, wherein the vector is a viral vector.

7. The method of claim 1, wherein the CpG-S motifs in the construct comprise a motif having the formula:

   $5' X_1CGX_2 3'$

   wherein at least one nucleotide separates consecutive CpGs, X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

8. The method of claim 7, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

9. The method of claim 7, wherein the motif comprises TCAACGTT.

10. The method of claim 7, wherein the motif comprises GTCG(T/C)T or TGACGTT.

11. The method of claim 7, wherein the motif comprises TGTCG(T/C)T.

12. The method of claim 7, wherein the motif comprises TCCATGTCGTTCCTGTCGTT.

13. The method of claim 7, wherein the motif comprises TCCTGACGTTCCTGACGTT.

14. The method of claim 7, wherein the motif comprises TCGTCGTTTTGTCGTTTTGTCGTT.

15. The method of claim 1, wherein the antigen is a viral antigen.

16. The method of claim 15, wherein the viral antigen is from Hepatitis B virus (HBV).

17. The method of claim 16, wherein the viral antigen is HBV surface antigen.

18. The method of claim 1, wherein the antigen is a bacterial antigen.

19. The method of claim 1, wherein the antigen is derived from a parasite.

20. The method of claim 1, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one antigenic polypeptide.

21. The method of claim 20, wherein the regulatory sequence is a promoter.

22. The method of claim 21, wherein the promoter is insensitive to cytokine regulation.

23. The method of claim 21, wherein the promoter is cytokine sensitive.

24.The method of claim 21, wherein the promoter is a non-viral promoter.

25.The method of claim 21, wherein the promoter is a viral promoter.

26. The method of claim 21, wherein the promoter is a tissue- or cell-specific promoter.

27. The method of claim 26, wherein the cell-specific promoter is operative in antigen-presenting cells.

28. The method of claim 27, wherein the promoter is a mammalian MHC I promoter.

29. The method of claim 25, wherein the promoter is a CMV promoter.

30. A method for stimulating a protective or therapeutic immune response to an antigen in a subject comprising:

administering to the subject an effective amount of a nucleic acid construct produced by determining the CpG-N and CpG-S motifs present in the construct; and

removing neutralizing CpG (CpG-N) motifs and optionally inserting stimulatory CpG (CpG-S) motifs in the construct,

thereby producing a nucleic acid construct having enhanced immunostimulatory efficacy and stimulating a protective or therapeutic immune response in the subject.

31. The method of claim 30, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one antigenic polypeptide.

32. The method of claim 30, wherein the construct is an expression vector.

33. The method of claim 31, wherein the regulatory sequence is a promoter.

34. The method of claim 33, wherein the promoter is insensitive to cytokine regulation.

35. The method of claim 33, wherein the promoter is cytokine sensitive.

36. The method of claim 33, wherein the promoter is a non-viral promoter.

37. The method of claim 33, wherein the promoter is a viral promoter.

38. The method of claim 33, wherein the promoter is a tissue-specific promoter.

39. The method of claim 33, wherein the promoter is a cell-specific promoter.

40. The method of claim 39, wherein the cell-specific promoter is operative in antigen-presenting cells.

41. The method of claim 40, wherein the promoter is a mammalian MHC I promoter.

42. The method of claim 37, wherein the promoter is a CMV promoter.

43. The method of claim 30, wherein the antigen is a viral antigen.

44. The method of claim 43, wherein the viral antigen is from Hepatitis B virus (HBV).

45. The method of claim 30, wherein the antigen is a bacterial antigen.

46. The method of claim 30, wherein the CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

47. The method of claim 32, wherein the vector is a plasmid.

48. The method of claim 32, wherein the vector is a viral vector.

49. The method of claim 30, wherein the CpG-S motifs in the construct comprise a motif having the formula:

$$5' X_1CGX_2 3'$$

wherein at least one nucleotide separates consecutive CpGs, X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

50. The method of claim 49, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

51. The method of claim 49, wherein the motif comprises TCAACGTT.

52. The method of claim 49, wherein the motif comprises GTCG(T/C)T or TGACGTT.

53.The method of claim 49, wherein the motif comprises TGTCG(T/C)T.

54. The method of claim 49, wherein the motif comprises TCCATGTCGTTCCTGTCGTT.

55.The method of claim 49, wherein the motif comprises TCCTGACGTTCCTGACGTT.

56. The method of claim 49, wherein the motif comprises TCGTCGTTTTGTCGTTTTGTCGTT.

57. The method of claim 30, wherein the antigen is derived from a parasite.

58. The method of claim 30, wherein the antigen is administered to the subject essentially simultaneously with the nucleic acid construct.

59. A method for enhancing the expression of a therapeutic polypeptide *in vivo* wherein the polypeptide is encoded by a nucleic acid contained in a nucleic acid construct comprising, determining the CpG-N and CpG-S motifs present in the construct, removing stimulatory CpG (CpG-S) motifs and/or inserting neutralizing CpG (CpG-N) motifs, thereby producing a nucleic acid construct providing enhanced expression of the therapeutic polypeptide.

60. The method of claim 59, wherein the CpG-S motifs are removed by site-specific mutagenesis.

61. The method of claim 59, wherein the CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

62. The method of claim 59, wherein the nucleic acid construct is an expression vector.

63. The method of claim 62 wherein the vector is a plasmid.

64.The method of claim 62, wherein the vector is a viral vector.

65. The method of claim 59, wherein the CpG-S motifs in the construct comprise a motif having the formula:

$$5' X_1CGX_2 3'$$

wherein at least one nucleotide separates consecutive CpGs, X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

66. The method of claim 65, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

67. The method of claim 65, wherein the motif contains TCAACGTT.

68. The method of claim 65, wherein the motif contains GTCG(T/C)T or TGACGTT.

69. The method of claim 65, wherein the motif contains TGTCG(T/C)T.

70. The method of claim 65, wherein the motif contains TCCATGTCGTTCCTGTCGTT.

71. The method of claim 65, wherein the motif contains TCCTGACGTTCCTGACGTT.

72. The method of claim 65, wherein the motif contains TCGTCGTTTTGTCGTTTTGTCGTT.

73. The method of claim 59, wherein the therapeutic polypeptide is selected from the group consisting of growth factors, toxins, tumor suppressors, cytokines, apoptotic proteins, interferons, hormones, clotting factors, ligands and receptors.

74. The method of claim 59, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one therapeutic polypeptide.

75. The method of claim 74, wherein the regulatory sequence is a promoter.

76. The method of claim 75, wherein the promoter is insensitive to cytokine regulation.

77. The method of claim 75, wherein the promoter is a non-viral promoter.

78. The method of claim 75, wherein the promoter is a viral promoter.

79.The method of claim 78, wherein the promoter is a CMV promoter.

80. The method of claim 75, wherein the promoter is a tissue- or cell-specific promoter.

81. The method of claim 80, wherein the tissue is muscle.

82. The method of claim 80, wherein the cell is a non-immune system cell.

83. The method of claim 59, wherein therapeutic nucleic acid sequence is an antisense nucleic acid sequence.

84. A method for enhancing the expression of a therapeutic polypeptide *in vivo* comprising administering to a subject a nucleic acid construct, wherein the construct is produced by determining the CpG-N and CpG-S motifs present in the construct and removing stimulatory CpG (CpG-S) motifs and/or inserting neutralizing CpG (CpG-N) motifs, thereby enhancing expression of the therapeutic polypeptide in the subject.

85. The method of claim 84, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one therapeutic polypeptide.

86. The method of claim 85, wherein the regulatory sequence is a promoter.

87. The method of claim 86, wherein the promoter is insensitive to cytokine regulation.

88. The method of claim 86, wherein the promoter is a non-viral promoter.

89. The method of claim 86, wherein the promoter is a viral promoter.

90. The method of claim 89, wherein the promoter is a CMV promoter.

91. The method of claim 86, wherein the promoter is a tissue- or cell-specific promoter.

92. The method of claim 91, wherein the tissue is muscle.

93. The method of claim 91, wherein the cell is a non-immune system cell.

94. The method of claim 84, wherein the CpG-S motifs are removed by site-specific mutagenesis.

95. The method of claim 84, wherein the CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

96. The method of claim 84, wherein the nucleic acid construct is an expression vector.

97. The method of claim 96, wherein the vector is a plasmid.

98. The method of claim 96, wherein the vector is a viral vector.

99. The method of claim 84, wherein the CpG-S motifs comprise a motif having the formula:

$5' X_1CGX_2 3'$

wherein at least one nucleotide separates consecutive CpGs, X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

100. The method of claim 99, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

101. The method of claim 99, wherein the motif contains TCAACGTT.

102. The method of claim 99, wherein the motif contains GTCG(T/C)T or TGACGTT.

103. The method of claim 99, wherein the motif contains TGTCG(T/C)T.

104. The method of claim 99, wherein the motif contains TCCATGTCGTTCCTGTCGTT.

105. The method of claim 99, wherein the motif contains TCCTGACGTTCCTGACGTT.

106. The method of claim 99, wherein the motif contains TCGTCGTTTTGTCGTTTTGTCGTT.

107. The method of claim 84, wherein the therapeutic polypeptide is selected from the group consisting of growth factors, toxins, tumor suppressors, cytokines, apoptotic proteins, interferons, hormones, clotting factors, ligands and receptors.

108. The method of claim 84, wherein therapeutic nucleic acid sequence is an antisense nucleic acid sequence.